Next-generation sequencing outpaces expectations

On January 8, Solexa, of Hayward, California, announced the completion of an early-access program evaluating its next-generation Genome Analysis system with customers and reiterated its intention to begin full commercial sales this quarter. Two months earlier, in anticipation of the entry of Solexa's technology and wanting a piece of the emerging market for whole-genome resequencing and analysis, San Diego, California–based microarray maker Illumina announced its intention to acquire the firm in a stock-for-stock transaction valued at around $600 million (*Nat. Biotechnol.* **25**, 10, 2007).

Next-generation sequencing is already several orders of magnitude more efficient than the Sanger capillary-array electrophoresis (CAE) machines that were the workhorse of the Human Genome Project.

On the completion of the merger, the new Solexa-Illumina business combination will join several other companies currently pushing the boundaries of sequencing technology. Curagen spin-off 454 Life Sciences, of Branford, Connecticut, and Agencourt Personal Genomics in Beverly, Massachusetts, a part of Applied Biosystems Group, are already on the market with systems that bring sequencing costs down several orders of magnitude below the millions of dollars per genome cost associated with capillary-array electrophoresis (CAE) sequencing—the technology that made possible the Human Genome Project a mere six years ago. Cambridge, Massachusetts–based Helicos Biosciences, for its part, claims that its single-molecule sequencing technology, expected to debut in the second half of the year, will enable the sought-after '$1,000 genome' price point, although not immediately. Smaller companies are also merging their respective technologies in an attempt to stay competitive in this technology race.

The intense activity in part stems from a pent-up and growing demand in both the research and clinical markets—the dynamic that Illumina identified in its discussions with customers, leading to the bid for Solexa. Indeed, the field appears to be advancing more rapidly than originally envisioned. According to John Sullivan, equity research analyst at Leerink Swann in Boston, the market for next-generation sequencing technology already stands at $1 billion, driven largely by targeted resequencing efforts aimed at finding genetic variations and rare mutations that contribute to complex diseases.

In 2004, the National Human Genome Research Institute (NHGRI) proposed a way to achieve affordable human genome sequencing by 2014, in two increments. NHGRI program director Jeff Schloss explains: "The way the [Requests for Applications] were laid out, at the time we launched the program, we were hoping the $100,000 genome might come in five years. The goal for $1,000 was to be five years after that." Solexa has already sequenced a gigabase at the $100,000 cost benchmark, making it the first company to announce the achievement of the first goal.

NHGRI wants the advantage of next-generation sequencing tools for its comparative genomics projects. The Cancer Genome Project, under the auspices of the National Institutes of Health, also suggests a nearly bottomless market for affordable gene sequencing. More speculatively, an affordable genome could make the dream of personalized medicine a reality, by enabling the sequencing of an individual's genome at a cost low enough to allow the information to become a routine part of one's medical record.

One of the newest winners of NHGRI's $100,000 genome grant, Intelligent BioSystems, of Waltham, Massachusetts, is developing a four-color sequencing-by-synthesis method using cleavable fluorescent nucleotide reversible terminators—an approach similar to that of Solexa. It is placing instruments in selected laboratories for beta testing, with a technology that features faster run cycles, less up-front expense and less costly implementation. "We're trying to design the system so that when the market is ready, it could actually be placed into a clinical laboratory," says CEO Steven Gordon. "The instrument cost is low enough that it could be used for clinical tests."

Companies have also started to win bids under the NHGRI $1,000 genome program. Unlike the $100,000 technologies, which focus on refining and improving existing methods, the conception of a $1,000 genome requires an entirely different paradigm—a discontinuous innovation. Helicos' technology, unlike the cluster-based approaches of 454, Agencourt and Solexa, could provide such a leap: in the first commercial award under the $1,000 program, it received, in October 2006, a $2 million grant to further develop its single-molecule approach.

According to Steve Lombardi, senior vice president of Marketing at Helicos, "If you had perfect chemistry, and each step was 99.99%, the instrument would generate 100 billion bases a day. The instrument is being designed for that throughput, but the first-generation chemistry will have a smaller yield—around 600 megabases per day." Improvements in chemistry could move Helicos to the $1,000 genome "in the first few years," he claims—well ahead of the NHGRI goal of 2014.

Over its three-year history, Helicos has raised $67 million in venture funding; the figure for Solexa was well over $100 million. Venture capitalists' appetite for these technologies is still strong. In December 2006, Pacific Biosciences of Menlo Park, California, raised $50 million in venture capital to further develop its single-molecule detection system, first published in 2003 (*Science* **299**, 682–686, 2003). Others are combining forces to gain the resources and technology breadth to compete. Also in December, NABsys, Inc. of Providence, Rhode Island, which has a $1,000 genome technology with a three-year delivery goal, according to CEO Barret Bready, acquired GeneSpectrum, merging its nanopore technology with GeneSpectrum's DNA hybridization technology to create hybridization-assisted nanopore sequencing.

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